PATENT
Our Docket: P-SE 3243

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of)
Al-Obeidi et al.)
)
Serial No: 09/211,715)
)
Filed: December 14, 1998)
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For: FACTOR Xa INHIBITORS)
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)

Asst. Commissioner for Patents
Washington, D.C. 20231

Examiner: F. Moezie

Group Art Unit: 1653

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C., 20231 on July 24, 2000.

By: James J. Wong
James J. Wong, Reg. No.: 34,949

July 24, 2000
Date of Signature

RESPONSE TO OFFICE ACTION

Responsive to the Office Action mailed March 23, 2000, entry of the following Amendments and Remarks is respectfully requested. A response to the Office Action was originally due June 23, 2000. Applicants submit herewith a Petition of Extension of Time to extend the time to reply to the Office Action for one month, until July 23, 2000. Accordingly, this Response is being timely filed.

REMARKS

Rejection of claims 1 to 3 under 35 U.S.C. 102(a) or (b)

Claims 1 to 3 are rejected under 35 U.S.C. 102(a) and/or (b) as being anticipated by U.S. Patent 5,721,214 to Marlowe et al, (hereafter referred to as "Marlowe '214) or 5,739,112 to Brunck et al (hereafter referred to as "Brunck '112").

EXHIBIT A

It is alleged in the Office action that each reference teaches peptides containing modified amino acids in their sequence, which exhibit activity against Factor Xa. The Office action notes the structures disclosed in the claims, presumably as being supportive of the alleged rejections. The Office action further notes that the present application is a continuation in part application, and that with the introduction of new subject matter, the effective date for the claims would have to be shown.

Marlowe '214 and Brunck '112 Are Not Available As References

Marlowe '214 issued on February 24, 1998, and has an effective U.S. filing date of June 7, 1995. Brunck '112 issued on April 14, 1998, and has an effective U.S. filing date of June 5, 1998.

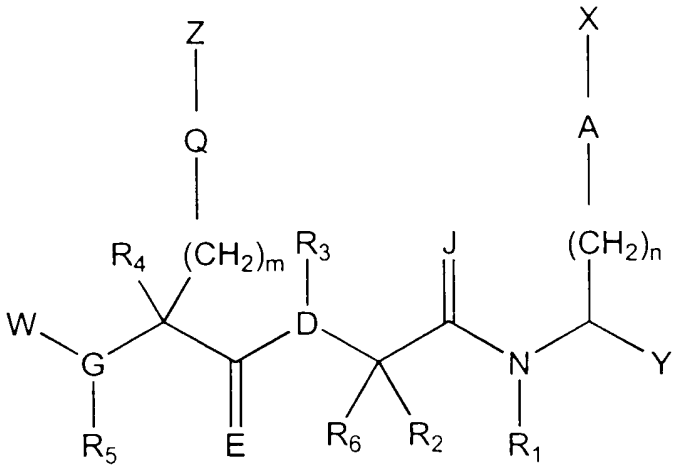
The present application was filed on December 14, 1998 as a continuation-in-part of United States Serial No. 08/947,794, filed October 8, 1997, which in turn was a continuation of prior application serial no. 08/428,404, filed April 25, 1995, which is a continuation-in-part of the parent patent application serial no. 08/233,054 ('054 application), filed April 26, 1994. A PCT application claiming priority to the '054 application was filed as PCT Application Number PCT/US95/05268, which was published as WO 95/29189.

Applicants' submit that the pending claims are entitled to the priority filing date the parent application, that is, the '054 application, whose filing date of April 26, 1994 antedates

the filing dates of Marlowe '214 and Brunck '112. Applicants' respectfully submit that the full scope of the claims in the present application are previously taught in the parent application. This is evidenced by the PCT Publication WO 95/291189 (copy attached as Exhibit A). Applicants' note that the title page of the PCT publication claims priority to the '054 application; Applicants' also note that claim 1 (at page 81) encompasses the full scope of the present claim in prosecution. Applicants' respectfully submit that the present application is entitled to the priority date of the '054 application. Therefore, the rejections based on Marlowe '214 and Brunck '112 should be withdrawn.

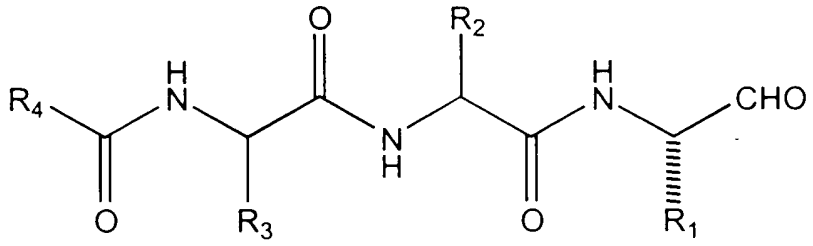
Applicants' further submit, however, that even if hypothetically, Marlowe '214 and Brunck '112 could be properly applied in the present case as references, the rejections are still improper.

Marlowe '214 discloses compounds, their salts and compositions having activity against mammalian factor Xa. The structures disclosed are depicted by the generic structure in claim 1,

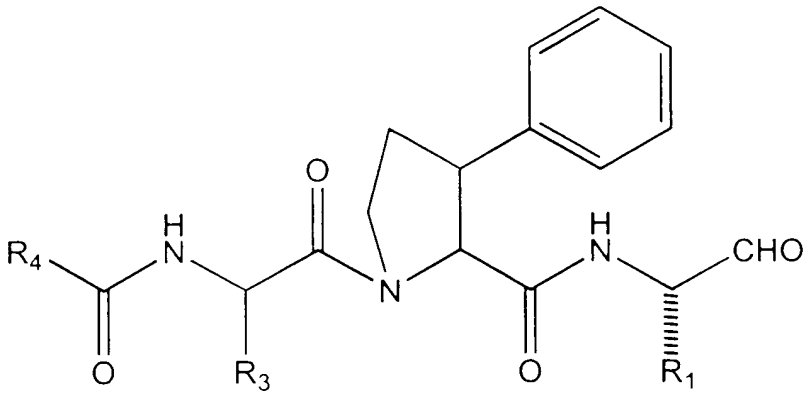


claim 1

Brunck '112 discloses compounds, salts and compositions having activity against mammalian factor Xa.
Brunck '112 discloses two tri-peptide structures derivatized at the C-terminus as aldehydes,

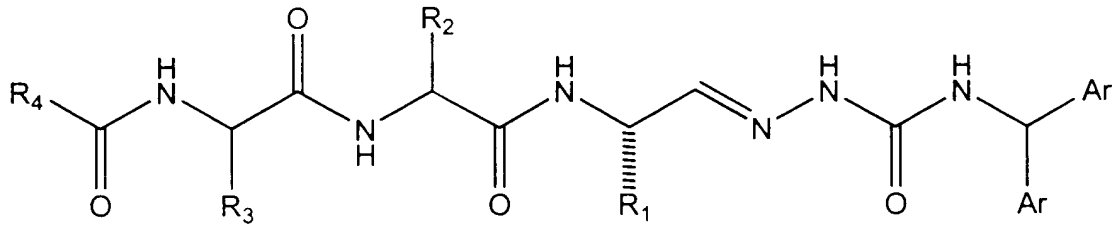


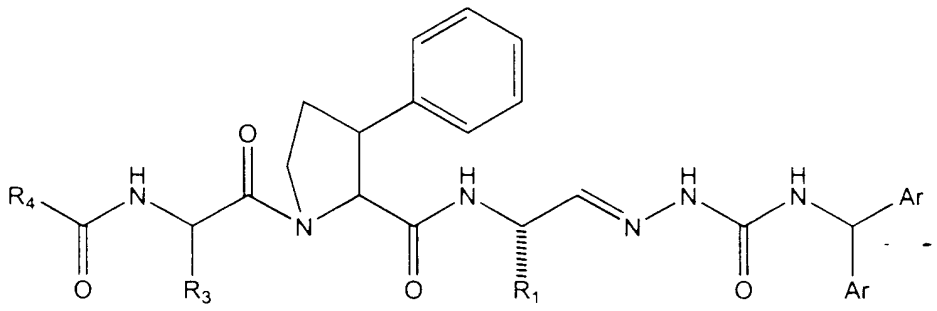
(I)



(Ia)

and as the corresponding semicarbazidyl-4-diphenylmethane derivatized intermediates (at col 11 to 16, and claim 1, col 44 to 45),as depicted as follows,





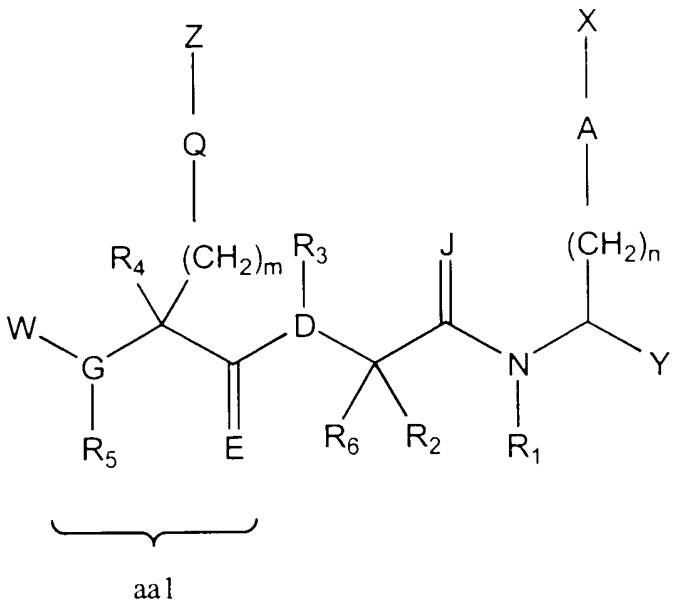
(II')

Presently Claimed Invention

The present invention is directed to non-naturally occurring compounds that specifically inhibit the activity of factor Xa, having the general formula A1-A2-$(A3)_m$-B, wherein m is 0 or 1. In the formula, A1, A2 and A3 each respectively represent the following, A1 is R_1-R_2-R_3; A2 is R_4-R_5-R_6; and A3 is R_7-R_8-R_9, where R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, and B are various chemical groups.

Marlowe '214 Does Not Anticipate The Present Invention

Marlowe '214 discloses substituted tri-peptides compounds having factor Xa activity. The N-terminus amino acid in Marlowe '214 is represent by aa1 in the following figure.



In Marlowe '214,

Q is piperdinyl, pyrrolidinyl, C_{3-8} cycloalkyl, phenyl, substituted phenyl, naphythyl, or pyridyl, or is absent; and

Z is NR'R", NH-C(NR'R")=NH, NH-C(NHR')=NR", S-C(NR'R")=NH, S-C(NHR')=NR", C(NR'R")=NH, C(NR'R")=NR", or CR'=NR",

where R' and R" are the same or different and are chosen from H, C_{1-6} alkyl, C_{1-3} arylalkyl, and aryl, or R'R" taken together represent $(CH_2)_p$, where p is an integer frm 2 to 5;

In the present invention tri-peptides are taught when m is 1; and R_1, R_3, R_4, R_6, R_7, and R_9 are appropriately substituted to teach the peptide backbone of the tri-peptide, where the groups R_1, R_2, and R_3 depict the amino acid at the N-terminus end of the

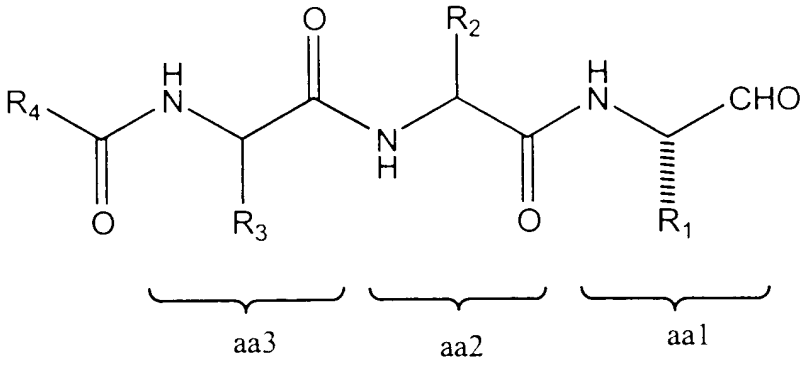
tripeptide. The groups at Q and Z in Marlowe '214 correspond to the position depicted as R_2 in the present invention, where

> *R_2 is $-CR_{99}R_{100}-$, wherein R_{99} and R_{100} independently are selected from the group consisting of an H, alkyl, arylalkyl, heteroarylalkyl and heteroaryl, and wherein R_{99} and R_{100} independently can be substituted with a substituent;*

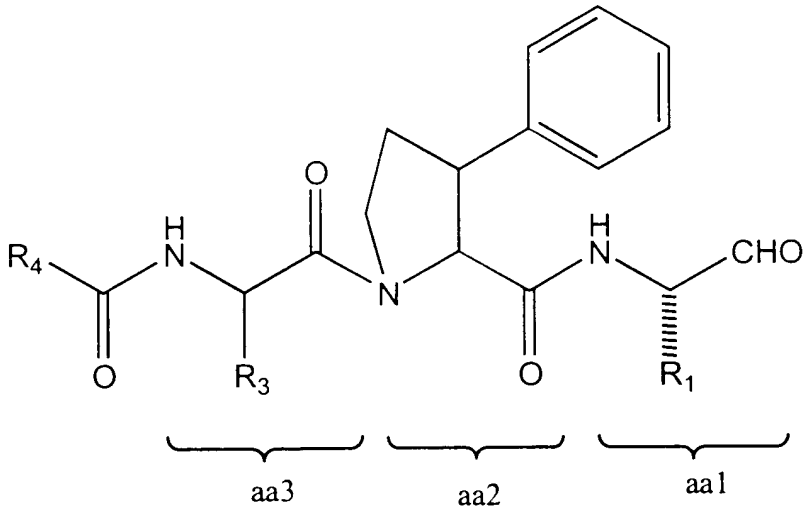
From the above comparison of Marlowe '214 and present invention, it is demonstrated that Marlowe '214 does not disclose, and therefore does not anticipate the present invention.

Brunck '112 Does Not Anticipate The Present Invention

Brunck '112 discloses a genus of tri-peptide structures, and a sub-genus where the second amino acid residue (aa2) is disclosed as proline.



(I)



(Ia)

Brunck '112 also discloses semicarbazidyl-4-diphenylmethane derivatized intermediates of the aforementioned tri-peptide at the C-terminus.

As noted above, the compounds of the present application are tri-peptides when m is 1; and R_1, R_3, R_4, R_6, R_7, and R_9 are appropriately substituted to depict the peptide backbone. A1 of the present application corresponds to the amino acid (aa1) at the N terminus disclosed in Brunck '112.

The C-terminus aldehyde group of the generic tri-peptide structure disclosed in Brunck '112 corresponds to the same position in a tripeptide as the combination of "B", and R_9 as a carbonyl in the present invention. It is demonstrated above, that Brunck '112 does not disclose, and therefore also does not anticipate the present invention.

Rejection of claims 1 to 11 under 35 U.S.C. 103(a)

Claim 1 to 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marlowe '214 and Brunck '112. As discussed above, Marlowe '214 and Brunck '112 do not anticipate the present invention. There is no disclosure in either Marlowe '214 or Brunck '112 which teach or suggest modifications to their disclosed structures so as to arrive at the compounds of the present invention. In addition, there were no arguments presented in the office action to point out how the instant rejection under 35 U.S.C. 103(a) is supported. Applicants respectfully submit that the rejection under 35 U.S.C. 103(a) should be withdrawn.

Double Patenting

Claim 11 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 39, line 40 of prior U.S. Patent No. 5,849,510.

Applicant respectfully submit that the Double patenting rejection should be held in abeyance until such time that the pending claims of the presention are allowed.

CONCLUSION

Applicants' have presented evidence as to unavailability of Marlowe '214 and Brunck '112 as references. In addition, Applicants' have presented arguments to the insufficiency of the 35 U.S.C. 102 and 103 rejections based on the aforementioned references, even if they could be properly asserted. Finally, Applicants' have requested that the double patenting rejection be held in abeyance until such time there are allowable claims in the present application.

In light of the Amendments and Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he/she is invited to call Cathryn Campbell or the undersigned attorney.

Respectfully submitted,

July 24, 2000
Date

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(54) Title: FACTOR Xa INHIBITORS

(57) Abstract

The invention provides compounds which specifically inhibit factor Xa activity. The compounds consist of the structure X_1-YIR-X_2, wherein X_1 is H, acyl, alkyl, acylalkyl, arylalkyl or one or more amino acids, and X_2 is a modified C-terminal group, one or more carboxy-protecting groups or one or more amino acids or other substituent, and Y, I and R are tyrosine, isoleucine and arginine, respectively, or peptidomimetic or organic structures that possess the same functional activity as Y, I and R, respectively. In addition, the present invention provides a compound having the structure A1-A2-$(A3)_m$-B, where m is 0 or 1. A compound of the invention can be linear or cyclic and can be about 2 and 43 residues in length. A compound of the invention is characterized, in part, in that it exhibits a specific inhibition of factor Xa activity with a K_i of $\leq$ 100 μM, preferably $\leq$ 2 nM, and does not substantially inhibit the activity of other proteases involved in the coagulation cascade. The invention further provides methods of specifically inhibiting the activity of factor Xa and of inhibiting blood clotting *in vitro* and in an individual and methods of detecting factor Xa levels or activity.

EXHIBIT A